PATENT
Attorney Docket No. 09404.0005-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Timothy John HENKEL	Group Art Unit: 1618
Application No.: 10/666,440	Examiner: M.P. YOUNG
Filed: September 19, 2003	Confirmation No.: 8311
For: METHODS OF TREATMENT	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDED APPEAL BRIEF UNDER BOARD RULE § 41.37

In accordance with Board Rule 41.37, and further to the Notice of Non-Compliant Appeal Brief mailed March 6, 2007, Appellants present this Amended Appeal Brief. This Amended Appeal Brief is due April 6, 2007, and is timely filed. Appellants provided a check for the fee of $500.00 required under 37 C.F.R. § 1.17(c) on January 5, 2007.

This Appeal Brief responds to the March 17, 2006, final rejection of claims 1 to 42, and to the Notice of Panel Decision from Pre-Appeal Brief Review mailed July 7, 2006.

If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to Deposit Account No. 06-0916.

Table of Contents

Real Party In Interest

LG Life Sciences Limited is the real party in interest as shown by the assignment recorded at Reel 014979, Frame 0039, in parent application 09/953,736, filed September 17, 2001.

Related Appeals and Interferences

There are currently no other appeals or interferences, of which Appellant, Appellant's legal representative, or Assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status Of Claims

This application, as originally filed on September 19, 2003, included claims 1-14.

The Office mailed a first Office Action on the merits on June 4, 2004. Claims 1-14 were rejected.

Appellants filed an Amendment and Request for Reconsideration on November 30, 2004, in which they requested entry of new claims 15-42. Original claims 1-14 remained pending and under consideration.

On August 10, 2005, the Office issued a non-final rejection of claims 1-42.

Appellants responded to the Aug. 10, 2005, Office Action with a Request for Reconsideration on December 8, 2005. No claims were canceled, amended, or added. Claims 1-42 remained pending.

The Office issued a final rejection of claims 1-42 on March 17, 2006.

On June 1, 2006, Appellants filed a Notice of Appeal and a Pre-Appeal Brief Request for Review. No claims were canceled, amended, or added. Claims 1-42 remained pending.

The Office on July 7, 2006, issued a Notice of Panel Decision from Pre-Appeal Brief Review in which it indicated that the Appeal should proceed.

In summary, claims 1-42 stand rejected and are on appeal. A list of the claims on appeal appears in the Claim Appendix that begins on page i.

Status Of Amendments

Appellant has not filed any Amendments After Final. The Amendment filed November 30, 2004, was entered. Office Action mailed Aug. 10, 2005, page 2.

Summary Of Claimed Subject Matter

The claimed subject matter relates to the use of gemifloxacin for reducing the recurrences or severity of recurrences of acute exacerbations of chronic bronchitis (AECB). Substitute Specification, page 2, lines 22-29. Thus, in one embodiment, claim 1 recites a method of reducing the recurrences of AECB in a patient in need thereof comprising administering a therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof. *Id.*, page 2, lines 22-25. In another aspect, claim 8 recites a method of reducing the severity of recurrences of AECB in a patient in need thereof comprising administering a therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof. *Id.*, page 2, lines 26-29. In some embodiments, the methods include conducting a long-term follow-up of the patient. *Id.*, page 10, lines 11-12. Claim 25 recites the method of claim 1, but includes this follow-up step. *Id.*, page 2, lines 22-25; page 10, lines 11-12. Similarly, claim 34 recites the method of claim 8, but includes the follow-up step. *Id.*, page 2, lines 26-29; page 10, lines 11-12.

In any of the methods, the gemifloxacin can be gemifloxacin mesylate, including gemifloxacin mesylate sesquihydrate. *Id.*, page 3, lines 1-2. Claims 2, 3, 9, 10, 27, 28, 32, 33, 36, 37, 41, and 42 recite those forms of gemifloxacin.

Both acute and elective treatments are described. *Id.*, page 3, lines 11-23. Thus, claims 4 and 11 recite that the treatment is acute, while claims 5 and 12 recite that the treatment is elective.

In certain embodiments, the gemifloxacin is administered orally once daily for 5 days, and the dosage can be 320 mg (calculated as the free base). *Id.*, page 4, lines 3-7. Claims 6, 13, 15-17, 21, 26, 31, 35, and 40 recite those aspects of the invention.

One particular group of patients that is at risk for AECB are those patients with chronic obstructive pulmonary disease (COPD). *Id.*, page 3, lines 17-19. Claims 7 and 14 recite that the patient suffers from COPD.

Many patients have multiple AECBs each year. Thus, in one embodiment, the methods of the invention involve patients who have had from 1 to 4 AECBs in the past year. *Id.*, page 8, Table 1. Claims 18-20 and 22-24 recite this aspect of the invention.

In those methods in which long-term follow-up is included as part of the method, that follow-up can be for a six month period following the start of gemifloxacin treatment, and may include clinical assessment during week 4-5, week 12, and week 26. *Id.*, page 5, lines 1-2 and 12-15. This aspect of the invention is recited in claims 29, 30, 38, and 39.

Grounds of Rejection

A. Claims 1, 4-8, 11-26, 34, and 35 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by File *et al.*, J. Chemotherapy, Vol. 12, pages 314-25 (August 2000) ("File").

B. Claims 2, 3, 9, 10, 27-33 and 36-42 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of File and WO 98/42705 to Kim *et al.* ("Kim").

Argument

I. Claims 1, 4-8, 11-26, 34, And 35 Are Patentable Over The File Reference Because It Is Not Available Under Any Section of 35 U.S.C. § 102

The Office first rejected claims 1, 4-8, 11-26, 34, and 35 as allegedly anticipated under 35 U.S.C. § 102(b) by the File reference in the Office Action mailed August 10, 2005. The Office asserts that File is available as a reference as of August 2000. Office Action mailed Aug. 10, 2005, page 2, ¶2.

As Appellants previously noted, this application claims benefit of provisional application no. 60/232,809, filed September 15, 2000, and provisional application no. 60/245,744, filed November 3, 2000. Consequently, File is not available as a reference under 35 U.S.C. § 102(b) since, even if it were available as of August 2000, that date is not more than one year before Appellant's earliest effective U.S. filing date. The Office has never asserted that Appellant is not entitled to benefit of the provisional application filing dates.

Further, Appellants respectfully submit that the Office has failed to establish that File was available to a member of the public before Appellant's earliest effective filing date. In particular, in the Request for Reconsideration filed December 8, 2005, Appellant provided evidence in the form of a date stamp that the library at the National Institutes of Health did not receive the Journal of Chemotherapy, volume 12, no. 4 until November 3, 2000. A copy of the evidence relied upon by Appellant and previously considered by the Office is attached to this Brief.

The Office has taken the position that the NIH date stamp is insufficient because "[u]nless conclusive evidence can be provided that the publisher of the article actively

withheld the volume 12 issue of the Journal of Chemotherapy, there is no evidence to support that the article was not available until November of 2000." Office Action mailed March 17, 2006, page 5. In addition, the Office also speculated that the reference may have been available on-line or with another library before November 2000, even though it provided no evidence in support of its position. *Id.* at 4-5.

In the Notice of Panel Decision from Pre-Appeal Brief Review, the Office stated that the "August 2000 publication date and print edition availability prior to Sept. 1, 2000 has been confirmed by communication with the publisher by our STIC library for the Fine reference." Appellants respectfully submit, however, that the e-mail from the publisher on which the Office relies does not provide evidentiary support for the Office's assertion. Instead, that e-mail states only that the File article "is in our archives on our website and the print edition was mailed to subscribers around September 1, 2000." Appellant respectfully traverses the Office's position because that e-mail does not provide any evidence that the File reference was received by a member of the public before Appellant's effective filing date.

It is the Office, not Appellant, that bears the burden of determining the issue or publication date of a reference so that a proper comparison between the application and reference dates can be made. M.P.E.P. 706.02(a)(I). As previously noted, a journal article is not available as prior art until it is received by a member of the public. M.P.E.P. § 2128.02 (emphasis added) (citing *In re Schlittler*, 234 F.2d 882, 110 U.S.P.Q. 304 (CCPA 1956)). Appellant has provided evidence in the form of a date stamp that File was not received by a member of the public until November 3, 2000.

That date stamp is the only evidence in the record regarding the date on which the File reference was received by a member of the public.

Further, while Internet disclosures and on-line databases can be relied upon by the Office, their date for the purposes of determining their availability as prior art is the date the item was publicly posted. M.P.E.P. 2128. If, however, the publication does not include a publication date (or retrieval date), it cannot be relied upon as prior art under 35 U.S.C. 102(a) or (b). *Id.* Here, the e-mail from the publisher does not establish a publication date, nor does it provide any evidence that the File reference was retrieved before Appellant's effective filing date.

The Office has not met its burden of showing that the File reference was available to a member of the public before Appellant's effective filing data. In contrast, Appellant has provided evidence that File was not publicly available until November 3, 2000. The File reference is not prior art under section 102(b). Nor is it prior art under 35 U.S.C. § 102(a), which requires that the reference describe the invention in a printed publication "*before* the invention thereof by the applicant for patent in the United States." 35 U.S.C. § 102(a) (emphasis added). The File article is therefore not available as a reference under any section of 35 U.S.C. § 102. Accordingly, Appellant respectfully requests that the Board reverse the rejection.

II. Claims 2, 3, 9, 10, 27-33 And 36-42 Are Patentable Over The Combination of File And Kim Because File Is Not Available As A Reference Under Any Section of 35 U.S.C. § 102

The rejection under 35 U.S.C. § 103(a) relies upon the teachings of File. For the reasons discussed in Section I, File is not available as a reference under any section of

35 U.S.C. § 102. Accordingly, it cannot be relied upon as a reference in a rejection under 35 U.S.C. § 103(a) and Appellant respectfully requests that this rejection also be reversed.

Conclusion

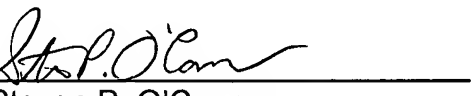
For the reasons given above, pending claims 1-42 are allowable and reversal of the Examiner's rejections is respectfully requested.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 15, 2007

By: 

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Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

1. A method of reducing the recurrences of acute exacerbations of chronic bronchitis (AECB) in a patient in need thereof comprising administering a therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1 comprising administering a therapeutically effective amount of gemifloxacin mesylate.

3. The method according to claim 2 comprising administering a therapeutically effective amount of gemifloxacin mesylate sesquihydrate.

4. The method according to claim 1 wherein gemifloxacin, or a pharmaceutically acceptable salt thereof, is administered as an acute treatment.

5. The method according to claim 1 wherein gemifloxacin, or a pharmaceutically acceptable salt thereof, is administered as an elective treatment.

6. The method according to claim 1 wherein gemifloxacin is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

7. The method according to claim 1 wherein the patient is suffering from chronic obstructive pulmonary disease.

8. A method of reducing the severity of recurrences of acute exacerbations of chronic bronchitis (AECB) in a patient in need thereof comprising administering a therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof.

9. The method according to claim 8 comprising administering a therapeutically effective amount of gemifloxacin mesylate.

10. The method according to claim 9 comprising administering a therapeutically effective amount of gemifloxacin mesylate sesquihydrate.

11. The method according to claim 8 wherein gemifloxacin, or a pharmaceutically acceptable salt thereof, is administered as an acute treatment.

12. The method according to claim 8 wherein gemifloxacin, or a pharmaceutically acceptable salt thereof, is administered as an elective treatment.

13. The method according to claim 8 wherein gemifloxacin is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

14. The method according to claim 8 wherein the patient is suffering from chronic obstructive pulmonary disease.

15. The method according to claim 4, wherein gemifloxacin is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

16. The method according to claim 11, wherein gemifloxacin is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

17. The method according to claim 1, wherein the therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof, is administered orally daily for five days.

18. The method according to claim 1, wherein the patient had from 1 to 4 AECBs in the last year.

19. The method according to claim 4, wherein the patient had from 1 to 4 AECBs in the last year.

20. The method according to claim 6, wherein the patient had from 1 to 4 AECBs in the last year.

21. The method according to claim 8, wherein the therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof, is administered orally daily for five days.

22. The method according to claim 8, wherein the patient had from 1 to 4 AECBs in the last year.

23. The method according to claim 11, wherein the patient had from 1 to 4 AECBs in the last year.

24. The method according to claim 13, wherein the patient had from 1 to 4 AECBs in the last year.

25. A method of reducing the recurrences of acute exacerbations of chronic bronchitis (AECB) in a patient in need thereof, comprising:

administering a therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof, to the patient, and

conducting a long-term follow-up of the patient;

thereby reducing the recurrences of AECB in the patient.

26. The method according to claim 25, wherein gemifloxacin or a pharmaceutically acceptable salt thereof is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

27. The method according to claim 26 comprising administering a therapeutically effective amount of gemifloxacin mesylate.

28. The method according to claim 27 comprising administering a therapeutically effective amount of gemifloxacin mesylate sesquihydrate.

29. The method according to claim 25, wherein the long-term follow-up is for a six month period following the start of gemifloxacin therapy.

30. The method according to claim 25, wherein the long-term follow-up comprises performing a clinical assessment of the patient during week 4-5, week 12, and week 26 following the start of gemifloxacin therapy.

31. The method according to claim 30, wherein gemifloxacin or a pharmaceutically acceptable salt thereof is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

32. The method according to claim 31 comprising administering a therapeutically effective amount of gemifloxacin mesylate.

33. The method according to claim 32 comprising administering a therapeutically effective amount of gemifloxacin mesylate sesquihydrate.

34. A method of reducing the severity of recurrences of acute exacerbations of chronic bronchitis (AECB) in a patient in need thereof, comprising:

administering a therapeutically effective amount of gemifloxacin, or a pharmaceutically acceptable salt thereof, to the patient, and

conducting a long-term follow-up of the patient;

thereby reducing the recurrences of AECB in the patient.

35. The method according to claim 34, wherein gemifloxacin or a pharmaceutically acceptable salt thereof is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

36. The method according to claim 35 comprising administering a therapeutically effective amount of gemifloxacin mesylate.

37. The method according to claim 36 comprising administering a therapeutically effective amount of gemifloxacin mesylate sesquihydrate.

38. The method according to claim 34, wherein the long-term follow-up is for a six month period following the start of gemifloxacin therapy.

39. The method according to claim 34, wherein the long-term follow-up comprises performing a clinical assessment of the patient during week 4-5, week 12, and week 26 following the start of gemifloxacin therapy.

40. The method according to claim 39, wherein gemifloxacin or a pharmaceutically acceptable salt thereof is administered orally at a dose of 320 mg (calculated as the free base) once daily for 5 days.

41. The method according to claim 40 comprising administering a therapeutically effective amount of gemifloxacin mesylate.

42. The method according to claim 41 comprising administering a therapeutically effective amount of gemifloxacin mesylate sesquihydrate.

Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

As part of the Response filed December 8, 2005, Appellants submitted the cover page of Vol. 12, No. 4 of the Journal of Chemotherapy, along with a copy of the first page of the first article in that journal (Papandreou et al.) and a copy of the article by File published at pages 314-325. The first page of the Papandreou article bears a date stamp showing that the National Institutes of Health received Vol. 12 of the Journal of Chemotherapy on November 3, 2000.

A copy of this evidence is attached to this Appeal Brief.

Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

There are no decisions in proceedings related to this appeal.

Volume 12, Number 4
August 2000

Journal of Geophysical Research

E.I.F.T. srl - Firenze

Journal of Chemotherapy Vol. 12 - n. 4 (267-273) - 2000

Multiantibiotic Resistance of Gram-Negative Bacteria Isolated from Drinking Water Samples in Southwest Greece

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Summary

In this study we monitored the sensitivity of 239 Gram-negative bacteria (of fecal and non-fecal origin), isolated from the old drinking water distribution network of Patras in southwestern Greece, to 20 antibiotic agents. Two methods were used to find the multiresistant bacteria (bacteria resistant to two or more antibiotics): the diffusion disk method and a serial dilution method. The Gram-negative bacteria tested were: *Enterobacteriaceae* (62), *Pseudomonas* (145), *Vibrionaceae* (24), *Chromobacter* (3), *Acinetobacter* (2) and others (4). The highest levels of antibiotic resistance were obtained for cephalothin (86.7%), ampicillin (77.5%) and carbenicillin (71%) followed by cefoxitin (55.4%) and cefuroxime (51.2%). Intermediate resistance levels were found for ticarcillin (31.3%), ceftizoxime (31.2%), chloramphenicol (30.3%), and cefotetan (25.2%). Low resistance levels were obtained for cefotaxime (17.9%), sulfisoxazole (15.2%), ceftriaxone (12.5%), tetracycline (11.9%), trimethoprim/sulfamethoxazole (7.4%) and piperacillin (2.4%). Overall 91.3% of the Gram-negative bacteria isolated from drinking water were multiresistant. No resistant strains were found to quinolones, aminoglycosides, imipenem, aztreonam, ceftazidime or cefoperazone. The high antibiotic resistance rate of the isolated microorganisms from the Patras drinking water supply is discussed.

Key words: **Antibiotic resistance, multiresistant bacteria, drinking water, Greece.**

INTRODUCTION

The occurrence of multiantibiotic resistant bacteria in the potable water of all municipal distribution systems has significantly increased [1,2,3,4,5]. The increase in bacterial pathogens observed in municipal water systems has been demonstrated in many studies and is significant

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Gemifloxacin versus Amoxicillin/Clavulanate in the Treatment of Acute Exacerbations of Chronic Bronchitis

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Summary

Six hundred patients were evaluated in this randomized, double-blind, double-dummy, multicenter, parallel-group study comparing the efficacy and safety of gemifloxacin (320 mg once-daily for 5 days) and amoxicillin/clavulanate (500/125 mg three-times daily for 7 days) for the treatment of acute exacerbations of chronic bronchitis (AECB). Of note, more than 90% of study participants had stage 2 disease at study entry. The two drugs were found to be equally effective, with clinical success rates of 93.6% for gemifloxacin and 93.2% on amoxicillin/clavulanate (95% CI -3.9 to 4.6). Bacteriological success rates favored gemifloxacin (90.9% compared with 79.5% for amoxicillin/clavulanate; 95% CI -3.3 to 26.0); however, this difference was not statistically significant. Gemifloxacin and amoxicillin/clavulanate were both well tolerated. In summary, gemifloxacin was found to be well tolerated and effective for the treatment of AECB, suggesting it is well suited for empirical treatment of this common respiratory condition in the current clinical environment.

Key words: **Gemifloxacin, amoxicillin/clavulanate, chronic bronchitis, efficacy, safety, clinical trial, fluoroquinolone, quinolone.**

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INTRODUCTION

Chronic bronchitis is frequently encountered in routine clinical practice, affecting as many as 15-21% of the adult population in the USA alone [1]. Chronic bronchial disease predisposes patients to frequent lower respiratory tract infection, with acute exacerbations of chronic bronchitis (AECB) accounting for approximately 12 million physician visits and 10% of hospital admissions annually [2,3]. Bacterial infection accounts for the majority of all AECB episodes, with *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis* being the predominant causative organisms in 85-95% of cases [4]. The most usual treatment approach is consequently empirical antibiotic therapy directed at these three pathogens.

Choice of appropriate antibacterial therapy for AECB is becoming more difficult, however, due to the increasing prevalence of antibiotic resistance in the principal causative pathogens. In the USA, for example, almost all clinical isolates of *M. catarrhalis* (>95%) and some 38% of *H. influenzae* isolates produce β-lactamases [5,6]. This results in resistance to some β-lactam antibiotics, most notably penicillin, and current estimates indicate a similar incidence of penicillin-resistance in *S. pneumoniae* (34%) [6]. The potential for cross-resistance between classes of antibacterial agents is a further concern, with available data demonstrating that many penicillin-resistant strains of *S. pneumoniae* will not be susceptible to oral cephalosporins and macrolides [6,7]. Although most data on antibiotic resistance are currently derived from North America, similar trends have been observed in Europe [8,9].

One approach to overcoming this problem has been to combine amoxicillin with a β-lactamase inhibitor such as clavulanic acid. Clavulanate-potentiated amoxicillin has proven clinical efficacy in the treatment of AECB [10-12], and has recently been shown to be one of the most cost-effective antibacterials currently available for the clinical management of this condition [13]. Experience gained over the past 18 years has established that amoxicillin/clavulanate has an excellent safety profile and minimal interaction potential. As a result, it has become the 'gold standard' against which newer antibacterials are judged [14].

Fluoroquinolones have also been shown to be effective for the treatment of AECB [11,15-19], although the efficacy of older drugs of this class, such as ciprofloxacin, may be limited by their low intrinsic activity against clinically important Gram-positive species, most notably *S. pneumoniae* [20]. Newer fluoroquinolones, such as trovafloxacin, have a much broader spectrum of antibacterial activity. However, the potential for serious adverse effects with trovafloxacin has limited its clinical utility [21,22].

Gemifloxacin is a novel, broad-spectrum fluoroquinolone, which appears to be well suited for the treatment of AECB, having potent *in vitro* activity against *H. influenzae* and *M. catarrhalis* as well as *S. pneumoniae* [23-25]. Importantly, gemifloxacin retains this potent antibacterial activity against β-lactam and macrolide-resistant strains [23,24], and is also active against isolates of *S. pneumoniae* and *H. influenzae* with decreased susceptibility to ciprofloxacin [26,27].

The aim of this study was to compare the clinical and bacteriological efficacy and tolerability of gemifloxacin in the treatment of AECB with that of amoxicillin/clavulanate. Both antibacterials were administered orally, with dosing regimens of 320 mg once-daily for 5 days and 500/125 mg three-times daily for 7 days, respectively.

PATIENTS AND METHODS

Patients

Male or female patients (age ≥40 years), with a history of chronic bronchitis characterized by cough and sputum production for more than 2 consecutive years and for most days in a period of 3 consecutive months, were considered for enrollment into this trial. All patients were required to have an acute exacerbation (defined as increased purulent sputum, cough and dyspnea) suitable for treatment with an oral antibacterial to be eligible for study participation.

Exclusion criteria included: serious underlying respiratory disease (such as pneumonia, cystic fibrosis, tuberculosis, bronchiectasis or active pulmonary malignancies); a history of epilepsy, convulsions or myasthenia gravis; a history of hemolytic crisis or known glucose-6-

phosphate dehydrogenase (G6PD) deficiency; and presence of any other complicating infection, disease or condition that might compromise evaluation of the study drugs (such as HIV infection, renal impairment, abnormal liver function tests, alcohol or drug abuse). Patients with known or suspected hypersensitivity to quinolone, penicillins or other β-lactam antibacterial agents, or a history of tendonitis while taking fluoroquinolones were also excluded, as were pregnant or nursing women. Patients must not have received another antibacterial agent within 7 days of study entry, been treated with an investigational drug, vaccine or device within the past month or participated in a previous study of gemifloxacin. Concurrent use of sucralfate, probecenid or systemic steroids (>10 mg/day prednisolone or equivalent) was prohibited.

Study design

This was a double-blind, double-dummy, multicenter, parallel-group study. Patients were randomized to receive either: oral gemifloxacin (Factive®; SmithKline Beecham Pharmaceuticals, Harlow, UK) 320 mg once-daily for 5 days with oral amoxicillin/ clavulanate-placebo three-times daily for 7 days; or, oral amoxicillin/clavulanate 500/125 mg (Augmentin®; SmithKline Beecham Pharmaceuticals, Harlow, UK) three-times daily for 7 days with oral gemifloxacin-placebo once-daily for 5 days.

Patients were assessed at five clinic visits over a period of approximately 5 weeks: screening (Day 0), on-therapy (Day 2-4), end of therapy (Day 9-11), follow-up (Day 14-21) and long-term follow-up (Day 28-35). Full medical history was recorded at screening, and a physical examination conducted. A chest X-ray film was obtained at this visit, or within 48 h of enrollment, to preclude a diagnosis of pneumonia. Patients were also required to have had forced expiratory volume in one second (FEV_1) measured within the previous 12 months. If not, an assessment was scheduled for between the end of therapy and long-term follow-up. Vital signs, clinical signs and symptoms of AECB were evaluated at all visits, and auscultatory assessments were made for wheeze, rales and crepitations. Peak expiratory flow (PEF) was evaluated at screening, follow-up and long-term follow-up.

Sputum samples were collected at screening and, where possible, at the end of therapy, follow-up and long-term follow-up, or at the time of study withdrawal. Sputum was assessed in a central laboratory by Gram-staining, routine microbiology culture, and susceptibility testing (performed according to National Committee for Clinical Laboratory Standards guidelines [28]). Purulence, assessed by microscopy, was defined as ≥25 white blood cells per field and ≤10 squamous epithelial cells at 100x magnification; a sputum sample was only considered evaluable if these criteria were met. Only organisms identified from evaluable samples were regarded as pathogenic.

The study was conducted in accordance with Good Clinical Practice guidelines and the revised Declaration of Helsinki (1996). An institutional review board (or ethics committee) approved the protocol at each center, and all patients provided written informed consent.

Efficacy assessments

The primary efficacy measure was clinical response at follow-up. Secondary efficacy measures included clinical response at end of therapy and at long-term follow-up, and bacteriological response at end of therapy, follow-up and long-term follow-up.

Clinical outcome was determined by comparing signs and symptoms of AECB (severity of cough and dyspnea, auscultatory findings, evaluation of sputum characteristics) with those from the previous visit. At the end of therapy, clinical outcome was classed as *clinical success* (sufficient improvement/resolution of signs and symptoms such that no additional antibacterial therapy was indicated), *clinical failure* (insufficient improvement/deterioration of signs and symptoms such that additional antibacterial therapy was indicated) or *unable to determine* (an assessment could not be made). Patients designated a clinical success at end of therapy were assessed at follow-up, and outcome was determined as *clinical success, clinical recurrence* (reappearance or deterioration of signs and symptoms such that additional antibacterial therapy was indicated) or *unable to determine*. Patients who were clinical successes at follow-up were assessed at long-term follow-up and outcome determined as *clinical success, clinical recurrence* or *unable to determine*.

Bacteriological outcome based on sputum culture and Gram-staining was assessed for each patient at the end of therapy and at both follow-up visits and classified as: *eradication* (elimination/continued absence of initial pathogen from a repeat sputum culture); *presumed eradication* (absence of an evaluable repeat sputum culture in a patient who was a clinical success); *bacterial persistence/recurrence* (presence of original pathogen on repeat culture at the end of therapy/initial pathogen eradicated, or presumed eradicated at previous visit but reappeared); *presumed bacterial persistence/recurrence* (absence of evaluable repeat culture in a patient who was a clinical failure/clinical recurrence); *unable to determine*. A new pathogen isolated from a symptomatic patient who required additional antibacterial therapy was considered a *superinfection* at the end of therapy and a *new infection* at follow-up or long-term follow-up. New pathogens identified in non-symptomatic patients not requiring additional antibacterial therapy were categorized as *colonization*.

The per-patient bacteriological response (only applicable to patients with at least one initial pathogen) was defined as a *success* if all initial pathogens were eradicated or presumed eradicated, with no evidence of superinfection or any new infections. Bacteriological *failure* was defined as persistence (documented or presumed) of one or more initial pathogens or superinfection at the end of therapy visit, and as recurrence of one or more initial pathogens or a new infection at either of the follow-up visits. An assessment of *unable to determine* was also considered as *bacteriological failure*.

Safety assessments

Adverse experiences were elicited by non-leading questioning at each visit. All adverse events were recorded by WHO body system and preferred term, and classified by severity (mild, moderate or severe) as well as presumed relationship to the study drug (not related, unlikely, suspected or probable). Patients reporting adverse experiences were followed up until the condition had subsided or stabilized. Laboratory tests for hematology, clinical chemistry and urinalysis were performed at screening, on-therapy and at the end of therapy.

Statistical analysis

Assuming an underlying equivalent clinical response rate of 88% at follow-up, 444 patients (222 in each treatment group) were required to give a power of 90% to detect that the lower limit of the two-sided 95% confidence interval (CI) for a difference in rates (gemifloxacin minus amoxicillin/clavulanate) was no less than -10% (indicating non-inferior efficacy of gemifloxacin) [29].

Efficacy analyses were performed on four different data-sets: the intent-to-treat (ITT) population, comprising all randomized patients who took at least one dose of study medication; the bacteriology ITT population, consisting of ITT patients who also had at least one pathogen identified at screening; the clinical per-protocol (PP) population, comprising all ITT patients who adhered to the study protocol; and the bacteriology PP population, which included all bacteriology ITT patients who did not violate the protocol. Patients with an outcome of unable to determine were excluded from the PP populations. Safety analyses were performed using the ITT population.

All efficacy variables were analyzed by unstratified comparison of proportions between treatment groups for the clinical PP population. Two-sided 95% CIs were used to estimate the difference in proportion of successes between treatments. The analysis was repeated for the ITT population and similar analyses were carried out for the secondary efficacy variables. All other intergroup differences were evaluated using Fisher's exact test.

RESULTS

Patients' characteristics

A total of 600 patients were enrolled into this study, of whom 304 were randomized to treatment with gemifloxacin and 296 to amoxicillin/clavulanate. All patients received at least one dose of study medication and were therefore included in the ITT population. A total of 287 and 275 patients from the two groups, respectively, completed the study. Reasons for the 38 withdrawals included adverse experiences (10 and 9 patients, respectively), protocol deviations (6 patients in each group), insufficient therapeutic effect (further antibacterial

treatment indicated; 1 patient in each group), lost to follow-up (4 patients treated with amoxicillin/clavulanate) and patient request (1 patient in the amoxicillin/clavulanate group).

The clinical PP population at follow-up comprised 268 patients who had received gemifloxacin and 266 treated with amoxicillin/clavulanate. Both the ITT and clinical PP follow-up populations were generally well matched for baseline demographics between the two groups, although slightly more males than females received amoxicillin/clavulanate (*Table 1*). While clinical characteristics and smoking history were also generally comparable between the two groups, a greater proportion of gemifloxacin-treated patients had expe-

TABLE 1 - *Patient characteristics at screening (ITT and clinical PP follow-up populations).*

Characteristic	ITT		Clinical PP follow-up	
	Gemifloxacin 320 mg od (n=304)	Amoxicillin/clavulanate 500/125 mg tid (n=296)	Gemifloxacin 320 mg od (n=264)	Amoxicillin/clavulanate 500/125 mg tid (n=266)
Gender, n. (%)				
Male	162 (53.3%)	177 (59.8%)	141 (53.4%)	157 (59.0%)
Female	142 (46.7%)	119 (40.2)	123 (46.6%)	109 (41.0%)
Age (years)				
Mean (SD)	64.2 (11.7)	64.0 (12.1)	64.1 (11.7)	63.8 (12.2)
Range	40-92	41-97	40-92	41-97
Weight (kg)				
Mean (SD)	72.1 (15.5)	74.2 (15.9)	72.5 (15.6)	74.5 (16.3)
Range	38-130	40-148	38-130	40-148
Race, n. (%)				
White	302 (99.3%)	293 (99.0%)	262 (99.2%)	263 (98.9%)
Duration of chronic bronchitis (years)				
Mean (SD)	13.6 (11.6)	13.6 (10.5)	13.5 (11.8)	13.5 (10.6)
Range	1.9-78.8	2.0-58.8	1.9-78.8	2.0-585.8
FEV_1 (% predicted), n. (%)				
<50%	104 (34.2%)	90 (30.4%)	91 (34.5%)	80 (30.1%)
50-70%	70 (23.0%)	80 (27.0%)	60 (22.7%)	73 (27.4%)
>70%	113 (37.2%)	111 (37.5%)	101 (38.3%)	102 (38.3%)
Unknown	17 (5.6%)	15 (5.1%)	12 (4.5%)	11 (4.1%)
Exacerbations treated with antibacterials in previous year, n. (%)				
0	19 (6.3%)	24 (8.1%)	17 (6.4%)	24 (9.0%)
1-4	226 (74.3%)	231 (78.0%)	193 (73.1%)	203 (76.3%)
>4	58 (19.1%)	41 (13.9%)	53 (20.1%)	39 (14.7%)
Unknown	1 (0.3%)	0	1 (0.4%)	0
Smoking history (n. of pack yrs), n. (%)				
0	96 (31.6%)	96 (32.4%)	88 (33.3%)	86 (32.3%)
>0-30	112 (36.8%)	113 (38.2%)	96 (36.4%)	103 (38.6%)
> 30	92 (30.3%)	82 (27.7%)	77 (29.2%)	73 (27.4%)
Unknown	4 (1.3%)	5 (1.7%)	3 (1.1%)	4 (1.5%)
Smoked regularly in past month, n. (%)				
Yes	103 (33.9%)	117 (39.5%)	90 (34.1%)	106 (39.8%)

rienced more than four exacerbations requiring antibacterial therapy in the year prior to study entry (19.1% versus 13.9% on amoxicillin/clavulanate for the ITT population, with similar proportions in the clinical PP follow-up population). Baseline FEV_1 was less than 50% of predicted in approximately one-third of patients in each treatment group. Most study participants were classified as having stage 2 AECB at study entry (90.8% versus 94.6% for the two groups, respectively; ITT population), with a further 8.9% of gemifloxacin-treated patients and 5.4% of those who received amoxicillin/clavulanate having severe, stage 3 disease.

Clinical efficacy

The clinical success rates at follow-up in the clinical PP population were 93.6% for gemifloxacin and 93.2% for amoxicillin/clavulanate. The 95% CI for the treatment difference was -3.9 to 4.6%, demonstrating that gemifloxacin was at least as effective as amoxicillin/clavulanate in terms of clinical response. Clinical success rates were 95.5% and 96.7% in the two groups, respectively, at the end of therapy and 87.2% and 87.4% at long-term follow-up (*Figure 1*). In all, 6.0% of gemifloxacin-treated patients and 5.5% of those who received amoxicillin/clavulanate experienced a clinical recurrence between the follow-up and long-term follow-up visits.

Clinical evaluation revealed a rapid improvement in signs and symptoms of AECB in both treatment groups on therapy. Similarly, there was a marked decrease in the proportions of patients with auscultatory findings on chest examination during the course of the study. The proportions of patients with wheeze decreased from 79.9% in the gemifloxacin group and 76.7% in the group randomized to amoxicillin/clavulanate at screening to 28.8% and 31.2%, respectively, at follow-up, with the proportions of patients with rales decreasing from 75.8% to 17.0% for gemifloxacin and from 82.8% to 18.0% for amoxicillin/clavulanate over the same period of time. Small but sustained improvements in pulmonary function were also apparent during the study. Percent predicted flow rate increased from 51.2% at screening to 56.2% at follow-up with gemifloxacin and from 50.9% to 60.3%, respectively, with amoxicillin/clavulanate.

Bacteriological efficacy

At least one pathogen was isolated at screening in 16.8% of patients in the gemifloxacin treatment group and 16.6% of those randomized to receive amoxicillin/clavulanate (ITT population). *M. catarrhalis* was the most prevalent pathogen, being isolated from 31.4% and 26.5% of patients in the two groups, respectively (bacteriology ITT population) (*Table 2*). *H. influenzae* was more commonly isolated in patients randomized to receive gemifloxacin, while *S. aureus* was more common in

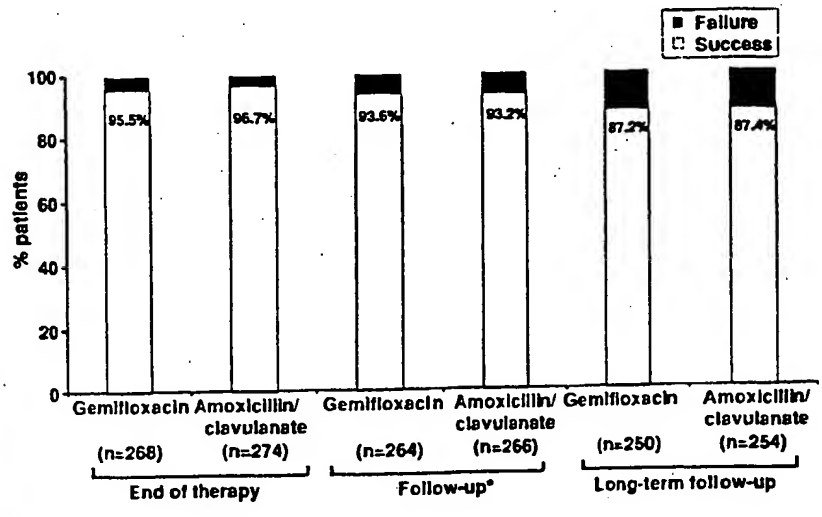

FIGURE 1 - Clinical success rates at the end of therapy, follow-up and long-term follow-up by treatment group (clinical PP population). *Primary efficacy parameter. 95% CI for treatment difference (gemifloxacin - amoxicillin/clavulanate) -3.9 to 4.6.

those assigned to amoxicillin/clavulanate. *Table 3* shows the susceptibilities of these key pathogens to the study drugs compared with those of a panel of other antibacterials, including quinolones, cephalosporins and macrolides. For each key pathogen, the minimum inhibitory concentrations (MICs) for gemifloxacin were generally the lowest of all antibacterials tested.

At screening, 93% of *M. catarrhalis* isolates were found to produce β-lactamase, as were 9.5% of *H. influenzae*, 50% of *H. parainfluenzae* and 91% of *S. aureus* isolates. Some 10.5% of *S. pneumoniae* isolated were found to be resistant to penicillin, with intermediate susceptibility documented in a further 16%. However, with the exception of a single *S. aureus* isolate, which was also resistant to methicillin, the MICs of gemifloxacin against all of these β-lactamase-producing or penicillin-resistant isolates remained low. The *S. aureus* exception had a gemifloxacin MIC of 4.0 μg/ml. Many initial pathogens also showed evidence of resistance to macrolide antibacterials (54% of *S. aureus*, 26% of *S. pneumoniae* and approximately 5% of *H. influenzae*). Again, the gemifloxacin MIC remained low against these macrolide-resistant isolates. Two *S. aureus* isolates were found to be resistant to some quinolone antibiotics; in both cases, gemifloxacin had the lowest MIC of all quinolones tested.

TABLE 2 - *Number of patients (%) with key pathogens associated with AECB at screening (bacteriology ITT population).*

Pathogen	Gemifloxacin 320 mg od (n=51)	Amoxicillin/clavulanate 500/125 mg tid (n=49)
M. catarrhalis	16 (31.4%)	13 (26.5%)
H. influenzae	13 (25.5%)	8 (16.3%)
S. pneumoniae	9 (17.6%)	10 (20.4%)
H. parainfluenzae	2 (3.9%)	0
S. aureus	1 (2.0%)	10 (20.4%)

Bacteriological response rates favored gemifloxacin at all time points (*Figure 2*). For the bacteriology PP population, the bacteriological success rates at follow-up were 90.9% for gemifloxacin and 79.5% for amoxicillin/clavulanate (95% CI -3.3 to 26.0). Similar findings

TABLE 3 - *In vitro susceptibilities (MIC_{90} in mg/ml, unless range is specified) of key pathogens isolated from the bacteriology ITT population to gemifloxacin, amoxicillin/clavulanate and other antibacterial agents.*

Antibacterial agent	*M. catarrhalis* (n=29)	*H. influenzae* (n=21)	*S. pneumoniae* (n=19)	*H. parainfluenzae* (n=2)	*S. aureus* (n=11)
Gemifloxacin	0.06	0.03	0.03	0.004–0.008	1
Amoxicillin/clavulanic acid*	1	0.5	2	0.5–2	8
Levofloxacin	0.25	0.5	1	0.03	4
Trovafloxacin	0.12	0.03	0.25	≤0.015–0.06	1
Ciprofloxacin	0.25	0.5	2	£0.015	16
Ofloxacin	1	1	2	≤0.06–0.12	16
Grepafloxacin	0.25	0.25	0.5	≤0.015–0.03	>16
Ampicillin	16	0.5	2***	0.5–64	>16
Cefuroxime	16	2	4	0.5–1	–
Clarithromycn	16	8	> 16	4–8	>16
Azithromycin	4	2	> 64	0.5–1	>64
Trimethoprim/sulphamethoxazole**	2	8	2	0.12–0.25	0.12
Gentamicin	–	–	–	–	0.25

* Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin ratio
** Trimethoprim/sulphamethoxazole was tested at a 1/19 ratio; MICs are expressed in terms of the trimethoprim concentration
*** Penicillin tested for *S. pneumoniae*

were observed at the end of therapy and at long-term follow-up. The majority of initial pathogens were eradicated or presumed eradicated at the end of therapy, follow-up and long-term follow-up visits in both treatment groups (*Figure 3*). Only three initial pathogens eradicated or presumed eradicated at the end of therapy were isolated again at follow-up (one isolate of *H. influenzae* in the gemifloxacin group and isolates of *Proteus mirabilis* and *Pseudomonas aeruginosa* in the amoxicillin/clavulanate group). One further isolate (*M. catarrhalis* from a gemifloxacin-treated patient) was presumed to have recurred at follow-up, on the basis of clinical failure in the absence of an evaluable sputum culture. Three pathogens in the gemifloxacin group and two in the amoxicillin/clavulanate group were presumed to have recurred at long-term follow-up. One patient in the gemifloxacin group was also

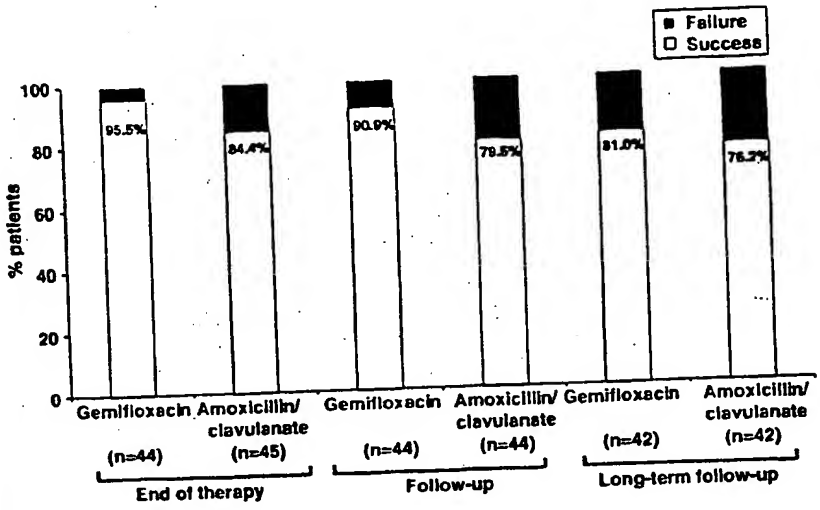

FIGURE 2 - Bacteriological success rates at the end of therapy, follow-up and long-term follow-up by treatment group (bacteriology PP population).

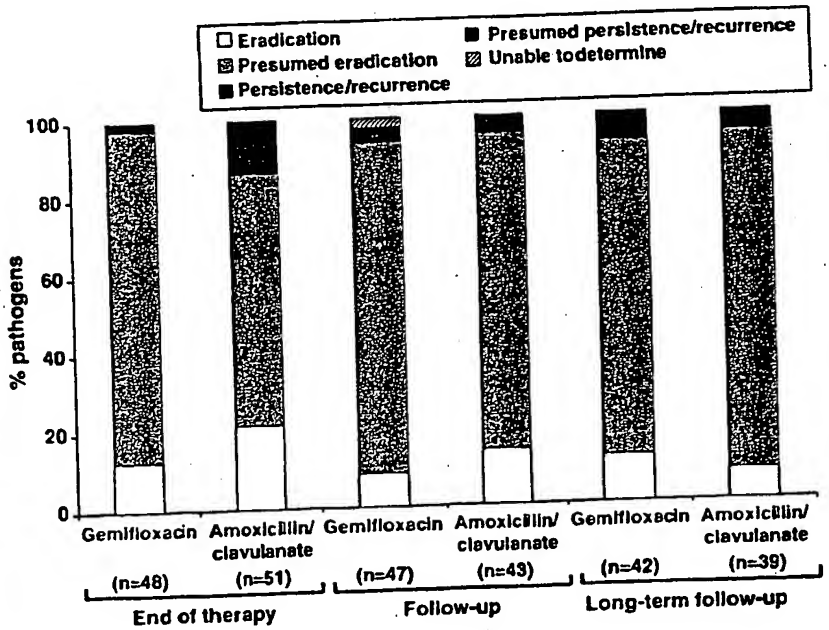

FIGURE 3 - Per-pathogen bacteriological outcome at the end of therapy, follow-up and long-term follow-up by treatment group.

found to have a superinfecting pathogen at the end-of-therapy visit (*P. aeruginosa*), with a new infection documented in another gemifloxacin-treated patient at long-term follow-up (*Enterobacter cloacae*).

Clinical or bacteriological failures could generally not be explained on the basis of MIC values for either of the study drugs, since these were typically low, particularly for gemifloxacin. The highest screening MIC value associated with subsequent treatment failure in the gemifloxacin group was seen in a patient with an initial isolate of *P. aeruginosa* with a MIC for gemifloxacin of 0.5 µg/ml. This patient, who also had an initial isolate of *S. pneumoniae* with a gemifloxacin MIC of 0.03 µg/ml, was a clinical and bacteriological success at the end of therapy, but a failure due to presumed bacteriological recurrence at the follow-up visit. A total of 9 patients treated with amoxicillin/clavulanate had isolates with MIC values ≥1 µg/ml for amoxicillin for either an initial pathogen at screening or persistent/recurrent pathogens or new infections associated with treatment failure (*Table 4*).

Safety

Ninety-five patients (31.3%) who received gemifloxacin and 104 (35.1%) of those treated with amoxicillin/clavulanate reported adverse experiences during the course of this study. Gastrointestinal disturbances were the most common adverse event in both treatment groups, occurring in 10.5% of gemifloxacin-treated patients and 18.9% of those on amoxicillin/clavulanate. The only adverse experience reported by at least 5% of patients in either treatment group was diarrhea, which was significantly more frequent with amoxicillin/clavulanate (11.5% compared with 2.3% for gemifloxacin; $p < 0.01$). Adverse experiences suspected or probably related to therapy were reported in 11.2% of gemifloxacin-treated patients and in 19.3% of patients in the amoxicillin/clavulanate group (*Table 5*).

The proportions of patients withdrawing from the study due to adverse experiences were comparable between the two treatment groups (3.3% for gemifloxacin and 3.0% for amoxicillin/clavulanate). No single adverse experience resulted in the withdrawal of more than one patient in the gemifloxacin group, while 5 patients treated with amoxicillin/clavulanate withdrew due to diarrhea.

TABLE 5 - *Number (%) of patients with adverse experiences suspected or probably related to the study medication (≥1% of patients).*

Adverse experience	Gemifloxacin 320 mg od (n=304)	Amoxicillin/clavulanate 500/125 mg tid (n=296)
Total	34 (11.2%)	57 (19.3%)
Nausea	8 (2.6%)	4 (1.4%)
Diarrhea	7 (2.3%)	31 (10.5%)
Dizziness	3 (1.0%)	3 (1.0%)
Abdominal pain	2 (0.7%)	3 (1.0%)
Vomiting	2 (0.7%)	3 (1.0%)
Dyspepsia	1 (0.3%)	4 (1.4%)

TABLE 4 - *Pathogens associated with clinical or bacteriological failure in either treatment group.*

Pathogen	N. of failures on amoxicillin/clavulanate	Amoxicillin/clavulanate MIC	N. of failures on gemifloxacin	Gemifloxacin MIC
P. aeruginosa	2	16->32 µg/ml	1*	0.5 µg/ml
P. mirabilis	2	1-4 µg/ml	-	-
S. pneumoniae	1	8 µg/ml	1*	0.03 µg/ml
H. influenzae	1	2 µg/ml	-	-
S. aureus	1	2 µg/ml	-	-
S. marcescens	1	>32 µg/ml	-	-
E. coli	1	8 µg/ml	-	-

* Pathogens isolated from a single patient

The proportions of patients reporting severe adverse experiences were similar in the two treatment groups (3.6% and 4.1%, respectively). The most frequently reported severe adverse events were dyspnea (3 patients) and headache (2 patients) for gemifloxacin, and bronchitis (3 patients) and diarrhea (2 patients) for amoxicillin/clavulanate. Serious adverse experiences occurred in 10 patients (3.3%) treated with gemifloxacin and in 5 (1.7%) of those who received amoxicillin/clavulanate. However, only one of these adverse experiences was suspected or probably related to the study medication (one case of insomnia with gemifloxacin). A total of 3 patients died during the course of the study, all from the gemifloxacin treatment group (2 patients due to respiratory insufficiency and 1 due to cardiac arrest), but none of these deaths were considered related to therapy.

Very few patients experienced vital signs of potential clinical concern during the course of the study (≤1%). The numbers of patients with liver function tests or other laboratory values of potential clinical concern were also low and similar in both treatment groups (<2%).

DISCUSSION

Results from this randomized, well-controlled clinical study clearly demonstrate that gemifloxacin (320 mg once-daily for 5 days) is as effective and well tolerated for the treatment of AECB as amoxicillin/clavulanate (500/125 mg three-times daily for 7 days). High clinical response rates were seen in both treatment groups approximately one week after the end of therapy (93.6% and 93.2%, respectively). The response rates seen in this study are comparable to those of other recently reported trials, some of which included antibacterials dosed more frequently or for longer durations than gemifloxacin (up to 10 or 14 days) [11,15-19,30]. The once-daily dosing regimen and short treatment duration of gemifloxacin does not therefore appear to compromise therapeutic efficacy and may in fact be expected to promote patient compliance with the treatment regimen [31], potentially reducing the risk of development of resistance in the target pathogens.

The most frequent pathogens isolated at screening in this study were *M. catarrhalis*, *H. influenzae*, *S. pneumoniae*, *H. parainfluenzae* and *S. aureus*, all of which are commonly associated with AECB of bacterial origin [4]. The growing incidence of resistance to β-lactam and macrolide antibiotics among these common respiratory pathogens is well documented [5-9]. In this study, almost 55% of baseline isolates showed evidence of b-lactam resistance, with about 15% also resistant to macrolides. In contrast, only two *S. aureus* isolates were found to have reduced susceptibility to quinolone antibiotics at baseline. Despite these underlying levels of antibacterial resistance, bacteriological response rates supported the clinical findings. Overall eradication rates for bacteriologically evaluable patients were also high, particularly in the gemifloxacin group. Most treatment failures could not be explained on the basis of the susceptibility of the initial pathogen, with gemifloxacin MICs generally much lower than those of the other antibacterial agents tested at baseline. The number of patients found to have positive sputum samples in this study was low (17% and 16% of patients in the gemifloxacin and amoxicillin/clavulanate treatment groups, respectively). A possible explanation for this is the transportation of sputum samples to the central laboratory for microbiological assessment. Ideally the sputum samples should have been immediately cultured at the study centers. This may also explain the apparent discrepancy in the rank order of pathogens from the expected of *H. influenzae*, *S. pneumoniae*, etc.

Recent safety concerns regarding the potential for serious adverse effects with trovafloxacin, one of the newer fluoroquinolones, have highlighted the need for a fluoroquinolone with enhanced Gram-positive activity and a favorable tolerability profile [21,22]. Gemifloxacin was well tolerated in this elderly population with chronic respiratory disease. Withdrawals due to adverse experiences were low in both treatment groups (approximately 3%), with gastrointestinal disturbances the most common adverse event seen in either arm. Only one serious adverse event was reported of suspected or probable relationship to the study drug (one case of insomnia in a gemifloxacin-treated patient). Very few patients had liver function tests or other laboratory values of potential clinical concern during the course of the study.

In summary, the results of this study suggest

that gemifloxacin administered orally once-daily for 5 days is effective and well tolerated as empirical therapy for the treatment of acute bacterial exacerbations of chronic bronchitis, providing a useful alternative to current standards of care.

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